PATENT SPECIFICATION

NO DRAWINGS

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866,681

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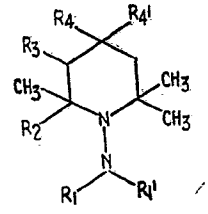
COMPLETE SPECIFICATION

N-Substituted Piperidines

We, MAY & BAKER LIMITED, a British Company, of Dagenham, Essex, England, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to heterocyclic compounds, and has for an object the provision of new and useful compounds which are therapeutically active substances for use in the treatment of hypertension or are intermediates for the preparation of such therapeutically active substances. Further objects are to provide useful processes for the preparation of, and pharmaceutical compositions containing, such compounds.

According to the present invention there are provided new piperidine and tetrahydropyridine derivatives of the general formula:



I

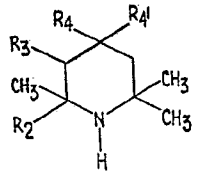
wherein R_1 represents a hydrogen atom or a methyl or ethyl group and R_1^1 represents a hydrogen atom, or R_1 and R_1^1 together represent a methylene group ($=CH_2$), an ethylidene group ($=CH.CH_3$) or an allylidene group ($=CH—CH=CH_2$), R_2 represents a hydrogen atom or a methyl group, R_4^1 represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms and R_3 and R_4 each represent a hydrogen atom or together represent a single bond, and acid addition salts thereof.

The compounds of general formula I and their acid addition salts are useful ganglion blocking agents and may consequently be used in the clinical treatment of hypertension.

Preferred compounds according to the invention are 1-amino-2,2,6,6-tetramethylpiperidine, 1 - methylamino - 2,2,6,6 - tetramethylpiperidine, 1 - methyleneamino-2,2,6,6 - tetramethylpiperidine, 1 - methylamino - 2,2,6,6 - tetramethyl - 1,2,5,6 - tetrahydropyridine, 1 - ethylideneamino - 2,2,6,6-tetramethylpiperidine, 1 - amino - 2,2,4,6,6-pentamethyl - 1,2,5,6 - tetrahydropyridine and their acid addition salts.

According to features of the invention the aforesaid new piperidines and tetrahydropyridines are prepared by the following methods:—

1. The compounds of formula I where R_1 and R_1^1 represent hydrogen atoms may be prepared from the compounds of the general formula:



II

(wherein the various symbols are as hereinbefore defined) by conversion into the corresponding *N*-amino compounds by known methods. For example, a compound of formula

II is converted into an *N*-nitroso-derivative by treatment with, for example, nitrous acid or with sodium nitrite in the presence of acid, followed by reduction of the nitroso group to amino by known methods, for example, using zinc and acetic acid, lithium aluminium hydride or electrolytic methods. Preferably, the reduction is effected by using zinc and acetic acid. An alternative process comprises the interaction of a compound of formula II with hydroxylamine-*O*-sulphonic acid.

The compounds of general formula II, some of which are known compounds, may be prepared from the corresponding 4-piperidones by known methods. For example those compounds where R_4 and R_4^1 are hydrogen atoms may be prepared by the direct reduction of the piperidones, with, for example, hydrazine and alkali in the presence of a high boiling alcohol. The compounds of formula II where R_4^1 represents an alkyl group containing 1 to 3 carbon atoms may be prepared by reacting the piperidone with a Grignard reagent of formula R_4^1MgX (where R_4^1 is an alkyl group of 1 to 3 carbon atoms and X is a halogen atom) followed by reduction or dehydration of the 4-piperidinol so produced to give a compound of formula II in which R_3 and R_4 represent hydrogen atoms or a single bond respectively.

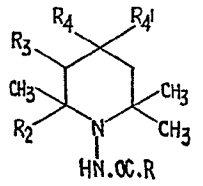
2. The compounds of general formula I where R_1 and R_1^1 together represent a methylene, ethylidene or allylidene group may be prepared from the compounds of formula I where R_1 and R_1^1 both represent hydrogen atoms by reaction with an aldehyde of formula $R_5.CHO$ (where R_5 represents a hydrogen atom or a methyl or vinyl group) or a derivative thereof, such as an acetal, thioacetal, diacyl derivative or bisulphite addition compound. The reaction is preferably carried out by mixing the reactants in an inert solvent with or without the addition of a dehydrating agent, and at room temperature or with gentle warming.

3. The compounds of formula I where R_1 represents a methyl or ethyl group and R_1^1 represents a hydrogen atom are prepared:

(a) by alkylation of compounds of formula I where R_1 and R_1^1 both represent hydrogen atoms by known methods for the conversion of a 1,1-disubstituted hydrazine to a 2-monoalkyl derivative, such methods including the employment of an alkylating agent in the form of a reactive ester such as methyl or ethyl iodide or methyl or ethyl-*p*-toluenesulphonate, each in the presence of an acid-binding agent, or

(b) by reduction of compounds of formula I where R_1 and R_1^1 together represent a methylene or ethylidene group by known methods. Preferably the reduction is carried out by hydrogenation in the presence of a catalyst such as Raney nickel, or

(c) by reduction of the acylamino compounds of the general formula:



III

(wherein R represents a hydrogen atom or a methyl group and the other symbols are as hereinbefore defined) by known methods for the reduction of a hydrazide to an *N*-alkylhydrazine. Preferably, the reduction is effected with lithium aluminium hydride. The compounds of formula III may be prepared by the acylation of a compound of formula I in which both R_1 and R_1^1 represent hydrogen atoms by known methods of acylation.

The expression "known methods" as used in this specification and in the appended claims means methods heretofore used or described in the chemical literature.

When, as is preferred, the compound of general formula I are used for therapeutic purposes in the form of acid addition salts, it should be understood that only those such salts should in practice be employed as contain anions that are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial physiological properties inherent in the parent compound are not vitiated by side-effects ascribable to those anions; in other words, only non-toxic salts are contemplated. Suitable acid addition salts include hydrohalides (for example hydrochlorides), phosphates, nitrates, sulphates, maleates, fumarates, citrates, tartrates, methane sulphonates and ethane disulphonates. These salts may be made from the bases of general formula I by the methods heretofore used in the art for making acid addition salts. For example, the acid addition salts may be made by mixing the required base with an equivalent quantity of a non-toxic acid in a solvent and isolating the resultant salt by filtration after, if necessary, evaporation of part or all of the solvent. They may be purified by crystallisation or by any other method commonly used in the art.

The invention is illustrated by the following Examples.

EXAMPLE I.

To a stirred mixture of 1-nitroso-2,2,6,6-tetramethylpiperidine (Franchimont and Friedmann, Rec. Trav. Chim. *24*, 415, (1905); 90 g.), water (500 ml.) and zinc dust (138 g.) was added 90% acetic acid (455 ml.) at such a rate to keep the temperature between 20 and 40° C. Stirring was continued for four hours after the addition was complete.

The reaction mixture was basified with concentrated sodium hydroxide solution and then steam distilled until the distillate was no longer basic. The distillate was treated with potassium hydroxide (200 g.) and the oil which separated was extracted with ether.

The ethereal solution was shaken with dilute acetic acid and after separation the aqueous layer was basified and extracted with ether. The ethereal extract was dried, freed of solvent and fractionally distilled. The fraction boiling at 59—65° C./8 mm. was collected and redistilled at 66—68° C./8 mm. to give 1 - amino - 2,2,6,6 - tetramethylpiperidine as a pale yellow liquid. Treatment of the base with ethereal hydrogen chloride gave the hydrochloride salt, m.p. 206—208° C.

EXAMPLE II.

To a stirred refluxing solution of 2,2,6,6-tetramethylpiperidine (71 g.) in water (30 ml.) was added dropwise during 10 minutes an ice-cold solution of hydroxylamine-*O*-sulphonic acid (6 g.) in water (15 ml.). The mixture was refluxed for a further 25 minutes, cooled, and basified with sodium hydroxide (15 ml. of 50% w/v solution). The alkaline solution was extracted with ether, and after drying, the extract was freed of solvent by evaporation. The residue was fractionally distilled *in vacuo*, and the fraction of b.p. 65—75° C., when examined by analytical gas-liquid chromatography, was shown to contain a proportion of 1-amino-2,2,6,6-tetramethylpiperidine. This compound was separated from the accompanying 2,2,6,6-tetramethylpiperidine by preparative gas-liquid chromatography on an Apiezon M/Celite column at 182° C., the emergent vapour fractions being collected in 2N hydrochloric acid. Evaporation and desiccation of the appropriate fraction gave 1 - amino - 2,2,6,6 - tetramethylpiperidine hydrochloride as a white solid, m.p. 206—208° C.

EXAMPLE III.

To a stirred refluxing mixture of lithium aluminium hydride (1.8 g.) in dry tetrahydrofuran (75 ml.) was added during 3 hours a solution of 1-nitroso-2,2,6,6-tetramethylpiperidine (8.5 g.) in dry tetrahydrofuran. The mixture was stirred and refluxed for a further 60 hours. After cooling, the reaction mixture was treated successively with water (1.67 ml.), sodium hydroxide (1.67 ml. of 15% w/v solution) and water (5.2 ml.). Inorganic material was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was shaken with acetic acid (40 ml. of 2N solution) and unchanged nitrosamine was separated by ether extraction. The aqueous solution was basified with sodium hydroxide (10 ml. of 50% w/v solution) and extracted with ether. The ethereal extract after drying and evaporation gave crude 1-amino-2,2,6,6-tetramethylpiperidine (3.0 g.) which was purified by fractional distillation *in vacuo*, b.p. 78—86° C./13 mm.

EXAMPLE IV.

A mixture of 1-amino-2,2,6,6-tetramethylpiperidine (6.24 g.), dry acetone (30 ml.), anhydrous potassium carbonate (6 g.) and methyl iodide (2.5 ml.) was heated under reflux for 16 hours. The suspension was filtered and freed of solvent. The filtrate was dissolved in ether (25 ml.) and a slight excess of aqueous-alcoholic hydriodic acid was added. The solid which separated was filtered, washed with ether, and recrystallised from water, to give 1-methylamino-2,2,6,6-tetramethylpiperidine hydriodide (4.8 g.) as white needles, m.p. 228—30° C. (dec.). The free base, obtained by basification of the hydriodide, is a colourless liquid, b.p. 84—87° C. at 17 mm. The hydrogen tartrate salt, prepared by addition of the base in ether to a warm alcoholic solution of tartaric acid, was obtained after equilibrating in air at 25° C. as a white microcrystalline monohydrate, m.p. 173—6° C.

EXAMPLE V.

A mixture of 1-amino-2,2,6,6-tetramethylpiperidine (20 g.), dry acetone (300 ml.), anhydrous potassium carbonate (120 g.) and ethyl iodide (30 g.) was stirred and boiled under reflux for 24 hours. The cooled mixture was diluted with dry ether (500 ml.) and filtered from inorganic material. The filtrate was freed of volatile materials by evaporation *in vacuo* at 40° C. Ether (50 ml.) was added to the residue, and the solution was extracted with acetic acid (4 portions of 30 ml. of 2N solution). The aqueous solution was basified with sodium hydroxide (40 ml. of 50% w/v solution) and extracted with ether. The extract was dried, and freed of solvent by evaporation *in vacuo* at 40° C. The residual oil was purified by preparative gas-liquid chromatography on an Apiezon M/Celite column at 182° C., the emergent vapour fractions being collected in 2N hydrochloric acid solution. (The word "Celite" is a Registered Trade Mark). Evaporation and desiccation of the appropriate fraction gave 1-ethylamino-2,2,6,6-tetramethylpiperidine hydrochloride (4 g.) as a white solid, m.p. 210—214° C., with previous shrinking.

EXAMPLE VI.

A mixture of 1-amino-2,2,6,6-tetramethylpiperidine (5.0 g.) and formaldehyde (3.0 ml. of 40% w/v solution) was shaken together for 10 minutes, the temperature rising spontaneously to 40° C. After cooling, the turbid solution was extracted with ether. The ethereal extract was dried and evaporated, and the residue was distilled *in vacuo*. 1-Methyleneamino - 2,2,6,6 - tetramethylpiperidine (3.6 g.) was obtained as a colourless liquid, b.p. 70° C./10 mm. Treatment of an ethereal solution of the base with alcoholic hydriodic acid gave the hydriodide salt as a

cream microcrystalline solid, m.p. 154° C. (dec.).

EXAMPLE VII.

To an ice-cooled solution of 1-amino-2,2,6,6-tetramethylpiperidine (5.0 g.), in ether (10 ml.) was added acetaldehyde (1.41 g.); heat was evolved and water began to separate. Dried magnesium sulphate (2 g.) was added and the mixture was allowed to stand at room temperature for 18 hours. The mixture was filtered and the ethereal filtrate evaporated. The residue was distilled *in vacuo* to give 1-ethylideneamino - 2,2,6,6 - tetramethylpiperidine (5.3 g.) as a colourless liquid, b.p. 73—77° C./10 mm. The hydriodide salt, prepared in a similar manner to that described in Example VI, was a white crystalline solid, m.p. 204—208° C.

EXAMPLE VIII.

To stirred ice-cooled hydrochloric acid (156 ml. of N solution), was added dropwise 2,2,6,6 - tetramethyl - 1,2,5,6 - tetrahydropyridine (21.7 g.). To the neutral solution was added a cold solution of sodium nitrite (10.8 g.) in water (100 ml.) during 90 minutes at below 5° C. The mixture was then boiled under reflux for 6 hours, a yellow oil separating. After cooling the solidified oil was extracted into ether. The extract was dried and freed of solvent by distillation, finally *in vacuo*, to give 1-nitroso-2,2,6,6-tetramethyl-1,2,5,6-tetrahydropyridine (21.2 g.) as a yellow solid, m.p. 50—52° C. after purification by sublimation *in vacuo*.

To a mixture of the above nitrosamine (23 g.), water (130 ml.) and zinc powder (37.5 g.) was added acetic acid (130 ml. of 90% w/v solution) dropwise during 4 hours, cooling being applied as necessary to keep the internal temperature below 45° C. The mixture was stirred for a further 16 hours at ambient temperature and then filtered). The filtrate was basified with sodium hydroxide (30 ml. of 50% w/v solution), and steam distilled until 300 ml. of distillate were collected. To the distillate was added potassium hydroxide (60 g.), and the cooled alkaline solution was extracted with ether several times. The ethereal solution was extracted with acetic acid (5 portions of 30 ml. of 50% w/v solution). The aqueous extract was basified with sodium hydroxide (30 ml. of 50% w/v solution), cooled in ice, and extracted with ether. The extract was dried, freed of solvent by distillation, and the residual oil purified by fractional distillation *in vacuo*. 1-Amino-2,2,6,6-tetramethyl-1,2,5,6-tetrahydropyridine (11.3 g.) was obtained as a colourless liquid, b.p. 83—85° C./10 mm. The hydriodide salt, prepared in ether by addition of alcoholic hydriodic acid, was a white crystalline solid, m.p. >300° C.

EXAMPLE IX.

A mixture of 1-amino-2,2,6,6-tetramethyl-1,2,5,6-tetrahydropyridine (5.5 g.) and formaldehyde (3.23 ml. of 40% w/v solution) was warmed at 50° C. for 30 minutes. The turbid solution was cooled, and extracted with ether. The extract was dried and freed of solvent by evaporation *in vacuo*. The residue was fractionally distilled *in vacuo* to give 1-methyleneamino - 2,2,6,6 - tetramethyl-1,2,5,6-tetrahydropyridine (3.9 g.) as a pale yellow liquid, b.p. 86—88° C./10 mm. The hydriodide salt, prepared by addition of alcoholic hydriodic acid to the base in ether, was a cream crystalline solid, m.p. 132—133° C. (dec.).

EXAMPLE X.

A solution of 1-methyleneamino-2,2,6,6-tetramethyl-1,2,5,6-tetrahydropyridine (1.2 g.) in methanol (15 ml.), containing Raney nickel catalyst (1 g.), was hydrogenated at 22° C. until the theoretical hydrogen uptake had taken place. The catalyst was separated by filtration and the filtrate was evaporated. The residual crude 1 - methylamino - 2,2,6,6 - tetramethyl-1,2,5,6-tetrahydropyridine (0.8 g.) was dissolved in ether, and treated with alcoholic hydriodic acid. The hydriodide salt separated as a crystalline solid, m.p. 219—223° C.

EXAMPLE XI.

2,2,6-Trimethyl-piperidine (37.9 g.) was added slowly to stirred hydrochloric acid (298 ml. of N solution) cooled in ice. To the neutral solution, sodium nitrite (20.6 g.) dissolved in water (200 ml.) was added over 30 minutes and the resulting mixture was refluxed for 10 hours.

The reaction mixture was steam distilled, and the distillate (2 l.) was saturated with salt and continuously extracted with ether for 24 hours. The ethereal extract was dried, and evaporated, and the residual oil purified by fractional distillation *in vacuo*. 1-Nitroso-2,2,6-trimethyl-piperidine (13.5 g.) was obtained as a yellow liquid, b.p. 130—133° C./10 mm.

To a stirred mixture of the above nitrosamine (13 g.), zinc dust (21 g.) and water (90 ml.), was added acetic acid (90 ml. of 90% w/v solution) at a rate to maintain the internal temperature below 40° C. Thereafter, the reaction mixture was stirred at ambient temperature for 16 hours and then filtered. The filtrate was basified with sodium hydroxide (25 ml. of 50% w/v solution) and steam distilled.

The distillate (500 ml.) was treated with potassium hydroxide (100 g.) and extracted with ether. The ethereal extract was extracted with an excess of dilute acetic acid, and after separation, the aqueous phase was basified and extracted with ether. The extract was dried and evaporated and the residue distilled *in vacuo*. 1 - Amino - 2,2,6 - trimethylpiperidine (4.9 g.) was obtained as a colourless oil, b.p. 62—68° C./13 mm.

EXAMPLE XII.

To a solution of 2,2,4,6-6-pentamethyl-

1,2,5,6-tetrahydropyridine hydriodide (28.1 g., prepared by the reaction of 2,2,6,6-tetramethylpiperid-4-one with methyl magnesium iodide in dry ether, and dehydration of the 2,2,4,6,6 - pentamethylpiperidin - 4 - ol so formed by the action of heat on its hydriodide) in water (300 ml.) at 50° C., was added a solution of sodium nitrite (6.9 g.) in water (30 ml.). The resulting mixture was refluxed for 16 hours, cooled, and extracted with ether. The extract was dried and evaporated, and the residue purified by distillation *in vacuo*. 1 - Nitroso - 2,2,4,6,6 - pentamethyl - 1,2,5,6-tetrahydropyridine (12.4 g.) was obtained as a dark yellow liquid, b.p. 136—140° C./10 mm.

To a mixture of the above nitrosamine (51.4 g.), zinc powder (83 g.) and water (288 ml.), was added acetic acid (288 ml. of 90% w/v solution) at a rate to maintain the internal temperature below 40° C. Thereafter, the reaction mixture was stirred at ambient temperature for 16 hours and filtered. The filtrate was basified with sodium hydroxide (50% w/v solution) and distilled in steam. The distillate (1 litre) was treated with potassium hydroxide (133 g.) and extracted with ether. The ethereal extract was extracted with an excess of dilute acetic acid and after separation the aqueous phase was basified and extracted with ether. The extract was dried and evaporated and the residue distilled *in vacuo*. 1 - Amino - 2,2,4,6,6 - pentamethyl - 1,2,5,6-tetrahydropyridine (15.9 g.) was obtained as a colourless liquid, b.p. 95—98° C./10 mm., the hydriodide of which is a cream solid, m.p. 160—163° C. (dec.).

EXAMPLE XIII.

1 - Amino - 2,2,4,6,6 - pentamethyl 1,2,5,6 - tetrahydropyridine (6.72 g.) was treated with formaldehyde as described in Example IX to give 1-methyleneamino-2,2,4,6,6 - pentamethyl - 1,2,5,6 - tetrahydropyridine (3.9 g.) as a colourless liquid b.p. 93—96° C./13 mm., the hydriodide of which is a white solid, m.p. 122—3° C. (dec.).

EXAMPLE XIV.

1 - Amino - 2,2,6,6 - tetramethylpiperidine (7.8 g.) was treated with acrolein (3.5 g.), when the temperature rose spontaneously to 40° C. and water separated. The mixture was warmed to 60° C. for 15 minutes, and after cooling it was diluted with ether and dried with magnesium sulphate. The mixture was filtered, and the solvent evaporated to give 1 - allylideneamino - 2,2,6,6 - tetramethylpiperidine as a yellow liquid, which partly resinified on attempting to distil a portion. The crude base in ether was treated with aqueous alcoholic hydriodic acid, and the precipitated solid, after trituration with ethyl acetate, was recrystallised from water, to give the hydriodide salt as a cream microcrystalline powder, m.p. 231° C. (dec.).

EXAMPLE XV.

1 - Amino - 2,2,6 - trimethylpiperidine (2.84 g.) was treated with formaldehyde as described in Example VI to give 1-methyleneamino - 2,2,6 - trimethylpiperidine (2.4 g.) as a colourless liquid, b.p. 78—81° C./13 mm., the hydriodide of which is a cream solid, m.p. 183—185° C.

EXAMPLE XVI.

A solution of 1-amino-2,2,6,6-tetramethylpiperidine (10.4 g.) in formic acid (50 ml.) was heated at 100° C. for 44 hours. Excess formic acid was removed by distillation, the residual solid was treated with excess 2N sodium hydroxide solution, and the resulting solution was extracted with ether. The ethereal extract was dried, and evaporated *in vacuo*. The solid residue was purified by sublimation *in vacuo* to give 1-formylamino-2,2,6,6-tetramethylpiperidine as a white solid, m.p. 124—7° C.

This formylamino compound (4 g.) was reduced in dry tetrahydrofuran (100 ml.) containing lithium aluminium hydride (1.65 g.). The mixture was stirred and allowed to react for a further 48 hours, and then treated successively with water (1.54 ml.), sodium hydroxide (1.54 ml. of 15% w/v solution) and water (4.84 ml.). Inorganic material was removed by filtration and the filtrate evaporated. Fractional distillation of the residue gave 1-methylamino-2,2,6,6-tetramethylpiperidine, identical with the material prepared as in Example IV.

The present invention includes within its scope pharmaceutical compositions which comprise one or more compounds of general formula I or their acid addition salts as aforesaid together with a significant amount of a pharmaceutical carrier. The invention includes especially such compositions made up for oral or parenteral administration. In clinical practice the compounds of the present invention will normally be administered orally so that compositions suitable for oral administration are preferred.

Solid compositions for oral administration include compressed tablets, pills, dispersible powders, and granules. In such solid compositions one or more of the active compounds of general formula I is or are admixed with at least one inert diluent such as calcium carbonate, potato starch, alginic acid, or lactose. The compositions may also contain, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents, such as magnesium stearate.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water and liquid paraffin. Besides inert diluents such compositions may also comprise adjuvants, such as wetting and sus-

pending agents, and sweetening and flavouring agents.

Compositions for oral administration include capsules of absorbable material such as gelatin containing one or more of the active substances of general formula I with or without the addition of diluents or excipients.

Preparations according to the invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. These compositions may also contain adjuvants such as wetting, emulsifying and dispersing agents. They may be sterilised by, for example, filtration through a bacteria-retaining filter, by incorporation in the compositions of sterilising agents, by irradiation, or by heating. They may also be manufactured in the form of sterile solid compositions, which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously several unit dosage forms may be administered at about the same time. In general, the preparations of the present invention should normally contain at least 0.025% by weight of active substance in the case of injectable solutions and at least 0.1% by weight of such substance in the case of oral preparations.

The following Examples will serve to illustrate pharmaceutical compositions according to the invention.

EXAMPLE XVII.

Tablets of the formula:

1-Amino-2,2,6,6-tetramethyl-piperidine hydrogen tartrate	2.5 mg.
Lactose	87.3 mg.
Maize Starch	5.0 mg.
Sodium carboxymethyl cellulose	0.2 mg.
Stearic acid	5.0 mg.

are prepared by dissolving 1-amino-2,2,6,6-tetramethylpiperidine hydrogen tartrate in water and dispersing the sodium carboxymethyl cellulose in the solution. The solution so obtained is then mixed with an intimate mixture of the lactose and starch and the resulting mass passed through a 12-mesh sieve. The resulting granules are dried overnight at 70° C. and then passed through a 16-mesh sieve. The stearic acid is added at this stage as a lubricant. These granules are then compressed into tablets.

EXAMPLE XVIII.

An injectable solution of the formula:

1-Amino-2,2,6,6-tetramethyl-piperidine hydrochloride	0.25 g.
Distilled water	up to 100 ml.

is prepared by dissolving the 1-amino-2,2,6,6-tetramethylpiperidine hydrochloride in the distilled water. The solution is filtered and filled into ampoules which are sterilised in an autoclave.

EXAMPLE XIX.

An injectable solution of the formula:

1-Methylamino-2,2,6,6-tetramethyl-piperidine hydrochloride	0.5 g.
Chlorocresol	0.2 g.
Distilled water	up to 100 ml.

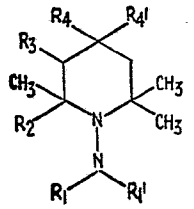
is prepared by dissolving the 1-methylamino-2,2,6,6-tetramethylpiperidine hydrochloride in the distilled water containing the chlorocresol and sterilising the solution by heating in an autoclave at a pressure of 10—15 lbs. per square inch during 30 minutes. There is thus obtained a sterile solution suitable for parenteral administration for therapeutic purposes.

EXAMPLE XX.

A mixture of 1-methyleneamino-2,2,6,6-tetramethylpiperidine hydrogen tartrate (10 g.) and calcium carbonate (70 g.) is granulated by admixture with a sufficient quantity of 10% aqueous maize starch paste. The granules are passed through an 8-mesh sieve and after drying at 50—55° C. they are then coated with a sufficient quantity of a solution of shellac (15 g.), castor oil (3 g.) and ethyl alcohol (800 g.). Magnesium stearate (3 g.) is then added to the granules after which the mixture is compressed to give tablets suitable for oral administration for therapeutic purposes.

WHAT WE CLAIM IS:—

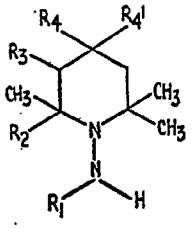
1. Compounds of the general formula:



where R_1 represents a hydrogen atom or a methyl or ethyl group and R_1^1 represents a hydrogen atom, or R_1 and R_1^1 together represent a methylene, ethylidene or allylidene group, R_2 represents a hydrogen atom or a methyl group, R_4^1 represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms and R_3 and R_4 each represent a

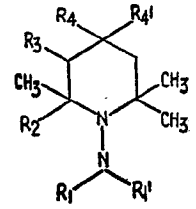
hydrogen atom or together represent a single bond.

2. An acid addition salt of a compound of the general formula:



where R_1 represents a hydrogen atom or a methyl or ethyl group, R_2 represents a hydrogen atom or a methyl group, R_4^1 represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms and R_3 and R_4 each represent a hydrogen atom or together represent a single bond.

3. An acid addition salt of a compound of the general formula:



where R_1 and R_1^1 together represent a methylene, ethylidene, or allylidene group, R_2 represents a hydrogen atom or a methyl group, R_4^1 represents a hydrogen atom or an alkyl group containing 1 to 3 carbon atoms and R_3 and R_4 each represent a hydrogen atom or together represent a single bond.

4. 1 - Amino - 2,2,6,6 - tetramethylpiperidine and its acid addition salts.

5. 1-Methylamino - 2,2,6,6 - tetramethylpiperidine and its acid addition salts.

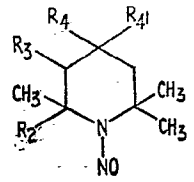
6. 1 - Methyleneamino - 2,2,6,6 - tetramethylpiperidine and its acid addition salts.

7. 1 - Methylamino - 2,2,6,6 - tetramethyl-1,2,5,6-tetrahydropyridine and its acid addition salts.

8. 1 - Ethylideneamino - 2,2,6,6 - tetramethylpiperidine and its acid addition salts.

9. 1 - Amino - 2,2,4,6,6 - pentamethyl-1,2,5,6-tetrahydropyridine and its acid addition salts.

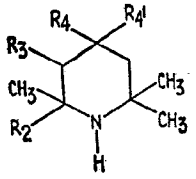
10. Process for the preparation of a compound as claimed in claim 1 where R_1 and R_1^1 represent hydrogen atoms which comprises reducing an *N*-nitroso compound of the formula:



(wherein the various symbols are as defined in claim 1) by known methods for the reduction of a nitroso group to an amino group.

11. Process according to claim 10 wherein the reduction is carried out with zinc and acetic acid.

12. Process for the preparation of a compound as claimed in claim 1 where R_1 and R_1^1 represent hydrogen atoms which comprises reacting a compound of the formula:



(wherein the various symbols are as defined in claim 1) with hydroxylamine-*O*-sulphonic acid.

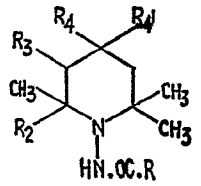
13. Process for the preparation of a compound as claimed in claim 1 where R_1 and R_1^1 together represent a methylene, ethylidene or allylidene group which comprises reacting a compound of the formula specified in claim 1 where R_1 and R_1^1 both represent hydrogen atoms with an aldehyde of the formula R_5.CHO (wherein R_5 is a hydrogen atom or a methyl or vinyl group) or a derivative thereof such as an acetal, thioacetal, diacyl derivative or bisulphite addition compound.

14. Proceess according to claim 13 wherein the reaction is effected in an inert solvent, with or without the addition of a dehydrating agent at room or slightly elevated temperature.

15. Process for the preparation of a compound as claimed in claim 1 where R_1 represents a methyl or ethyl group and R_1^1 represents a hydrogen atom which comprises alkylating a compound of the formula specified in claim 1 where R_1 and R_1^1 both represent hydrogen atoms by known methods for the conversion of a 1,1-disubstituted hydrazine to a 2-monoalkyl derivative.

16. Process according to claim 15 wherein the alkylation is effected with a reactive ester, such as methyl or ethyl iodide.

17. Process for the preparation of a compound as claimed in claim 1 where R_1 represents a methyl or ethyl group and R_1^1 represents a hydrogen atom which comprises reducing a compound of the formula:



(wherein R represents a hydrogen atom or a methyl group and the other symbols are as defined in claim 1) by known methods for the reduction of a hydrazide to an N-alkylhydrazine.

18. Process according to claim 17 wherein the reduction is effected with lithium aluminium hydride in an inert solvent.

19. Process as claimed in any of claims 10 to 18 when carried out substantially as described in any one of Examples I to XVI.

20. Compounds as claimed in claim 1 when prepared by a process claimed in any one of claims 10 to 19.

21. A pharmaceutical composition comprising one or more compounds or acid addition salts thereof as claimed in any one of claims 1 to 9 and 20 in association with a significant amount of a pharmaceutical carrier.

22. A pharmaceutical composition as claimed in claim 21 substantially as described in any one of Examples XVII to XX.

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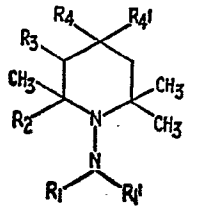
PROVISIONAL SPECIFICATION
No. 16551 A.D. 1598

N-Substituted Piperidines

We, MAY & BAKER LIMITED, a British Company, of Dagenham, Essex, England, do hereby declare this invention to be described in the following statement:—

This invention relates to heterocyclic compounds, and has for an object the provision of new and useful compounds which are therapeutically active substances for use in the treatment of hypertension or are intermediates for the preparation of such therapeutically active substances. Further objects are to provide useful processes for the preparation of, and pharmaceutical compositions containing, such compounds.

According to an aspect of the present invention, there are provided new and useful piperidine derivatives of the general formula:

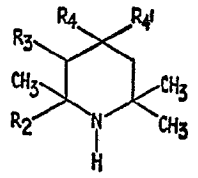


I

wherein R_1 and R_1^1 each represent a hydrogen atom or a lower alkyl group, R_2 represents a hydrogen atom or a methyl group, R_4^1 represents a hydrogen atom or a lower alkyl group and R_3 and R_4 may each represent a hydrogen atom or together represent a single bond, and acid addition and quaternary ammonium salts thereof.

These piperidine compounds have a powerful ganglion blocking activity which renders them extremely useful in the treatment of hypertension. Of importance are those compounds in which R_2 is a methyl group, and R_4^1 is a hydrogen atom or a methyl or ethyl group. Particular compounds of outstanding importance are 1-amino, and 1-methylamino 2:2:6:6-tetramethylpiperidine and their salts which have been found to be more active as ganglion blocking agents than the known hexamethonium compounds.

According to a feature of the present invention, the new piperidine derivatives of general formula I wherein R_1 and R_1^1 represent hydrogen atoms are prepared from a corresponding piperidine compound of the formula:



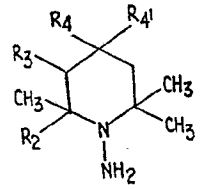
II

(wherein the various symbols are as hereinbefore defined) by conversion into the corresponding N-nitroso derivative by treatment with, for example, nitrous acid or with sodium nitrite in the presence of acid, followed by reduction of the nitroso group to amino by known methods, for example using zinc and acetic acid, lithium aluminium hydride or electrolytic methods. An alternative process comprises the interaction of a piperidine compound of formula II with hydroxylamine-*O*-sulphonic acid.

The piperidines of general formula I wherein one of R_1 and R_1^1 represents a lower alkyl group and the other represents a hydrogen atom may be prepared, in accord-

ance with further features of the invention, by the following processes:

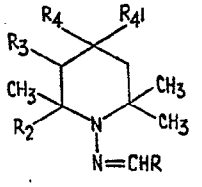
(1) Alkylation of a 1-aminopiperidine of the formula:



III

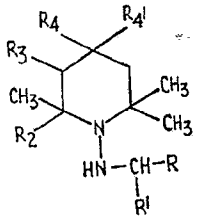
(wherein the various symbols are as hereinbefore defined) by known methods for the conversion of a 1:1-disubstituted hydrazine to its 2-alkyl or 2:2-dialkyl derivative. Such methods include the employment of an alkylating agent in the form of a reactive ester such as methyl iodide or methyl *para*-toluenesulphonate, each in the presence of an acid binding agent.

(2) Conversion of a 1-aminopiperidine conforming to formula III to an alkylidene derivative by treatment with an aldehyde RCHO (where R represents a hydrogen atom or an alkyl group) and reaction of the resultant alkylidene derivative of the formula:



IV

(wherein the various symbols are as hereinbefore defined) with a Grignard reagent R^1MgX (wherein R^1 is an alkyl group such as the grouping $-CH(R)-R^1$ represents the lower alkyl group R_1) to give a 1-monoalkylaminopiperidine of the formula:



V

For therapeutic purposes, the compounds of formula I may be employed in the form of their salts, it being understood that only those such salts should in practice be employed as contain anions or radicals that are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial physiological properties inherent in the parent compound are not vitiated by side-effects ascribable to those anions or radicals. Suitable acid addition salts include hydrohalides, for example, hydrochlorides, 8-chlorotheo-phyllinates, phosphates, nitrates, sulphates, maleates, fumarates, citrates, tartrates, methanesulphonates, and ethanedisulphonates. Suitable quaternary ammonium derivatives include those prepared from organic halides, for example, methyl or ethyl iodide, chloride, or bromide or allyl or benzyl chloride or bromide.

The invention is illustated by the following Examples.

EXAMPLE I.

To a stirred mixture of 1-nitroso-2:2:6:6-tetramethylpiperidine (Franchimont and Friedmann, Rec. Trav. Chim. *24*, 415 (1905); 90 g.), water (500 ml.) and zinc dust (138 g.) was added 90% acetic acid (455 mls.) at such a rate to keep the temperature between 20 and 40° C. Stirring was continued for four hours after the addition was complete.

The reaction mixture was basified with concentrated sodium hydroxide solution and then steam distilled until the distillate was no longer basic. The distillate was treated with potassium hydroxide (200 g.) and the oil which separated was extracted with ether.

The ethereal solution was shaken with dilute acetic acid and after separation the aqueous layer was basified and extracted with ether. The ethereal extract was dried, freed of solvent and fractionally distilled. The fraction boiling at 59—65° C./8 mm. was collected and redistilled at 66—68° C./8 mm. to give 1-amino-2:2:6:6-tetramethylpiperidine as a pale yellow liquid. Treatment of the base with ethereal hydrogen chloride gave the hydrochloride salt, m.p. 206—208° C.

EXAMPLE II.

A solution of 1-amino-2:2:6:6-tetramethylpiperidine (1.8 g.) in dry benzene (25 ml.) was treated with methyl iodide (0.74 ml.) and allowed to stand four four days. The crystalline hydriodide of 1-methylamino-2:2:6:6-tetramethylpiperidine which separated was purified by recrystallisation from acetone containing a little methanol. It did not melt below 300° C.

The present invention also provides as a still further feature pharmaceutical compositions comprising one or more of the compounds of fomula I, or a salt thereof, and a significant amount of a pharmaceutical carrier which may be either a solid material or a liquid. In clinical practice the compounds of the present invention will normally be administered orally, in consequence of which the preferred formulations are those of the kind suitable for oral administration.

Preparations for oral ingestion can be liquids or solids or any combination of these forms, such as solutions, suspensions, syrups, elixirs, emulsions, powders or tablets. Pharmaceutical preparations for administration of the active therapeutic agents in unit dose form can take the form of compressed powders (or tablets) or of a powder enclosed in a suitable capsule of absorbable material such as gelatin. These compressed powders (or tablets) can take the form of the active materials admixed with suitable excipients and/or diluents such as starch, lactose, stearic acid, magnesium stearate or dextrin.

In yet a further embodiment, the active material may, as such or in the form of a diluted composition, be put up in powder packets and employed as such.

Preparations for parenteral administration may be sterile solutions or suspensions in water or other liquids, with or without the addition of soluble or insoluble diluents and/or solid or liquid excipients.

The percentage of active ingredient in the composition of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously several unit dosage forms may be administered at about the same time. In general, the preparations of the present invention should normally contain at least 0.025% by weight of active substance in the case of injectable solutions and at least 0.1% by weight of such substance in the case of oral preparations.

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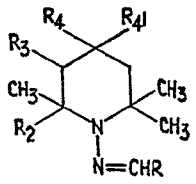
PROVISIONAL SPECIFICATION
No. 12303 A.D. 1959

N-Substituted Piperidines

We, MAY AND BAKER LIMITED, a British Company, of Dagenham, Essex, England, do hereby declare this invention to be described in the following statement:—

This invention relates to heterocyclic compounds and has for an object the provision of new and useful compounds which are therapeutically active substances for use in the treatment of hypertension or are intermediates for the preparation of such therapeutically active substances. Further objects are to provide processes for the preparation of, and pharmaceutical compositions containing, such compounds.

According to the present invention there are provided new and useful heterocyclic compounds of the general formula:

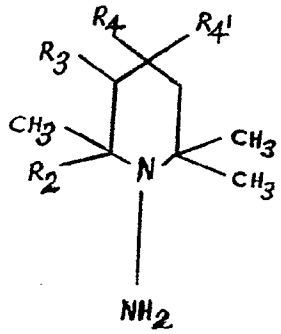


I

(wherein R represents a hydrogen atom, or a methyl group or vinyl group, R_2 represents a hydrogen atom or a methyl group, R_4^1, represents a hydrogen atom or a lower alkyl group and R_3 and R_4 may each represent a hydrogen atom or together represent a single bond and acid addition salts thereof.

These piperidine and tetrahydropyridine derivatives have a powerful ganglion blocking activity which renders them extremely useful in the treatment of hypertension. Of importance are those compounds in which R_2 is a methyl group and R_4^1 is a hydrogen atom or a methyl or ethyl group. Of outstanding importance as ganglion blocking agents are 1-methyleneamino - 2,2,6,6 - tetramethylpiperidine and its acid addition salts.

According to a feature of the present invention, the new heterocyclic compounds of general formula I are prepared by the reaction of a 1-aminopiperidine of 1-aminotetrahydropyridine of the formula:—



II

(wherein the various symbols are as hereinbefore defined) with an aldehyde of formula RCHO (wherein R is as hereinbefore defined) as such or in the form of a reactive derivative thereof (such as an acetal). The reaction is preferably carried out by mixing the reactants in an inert solvent with or without the addition of a dehydrating agent, and at room temperature or with gentle warming.

The compounds of formula I can be used as intermediates for the production of other hypotensive agents as described in the Specification of co-pending Application No. 16551/

58. The said specification also describes the preparation of the compounds of formula II.

For therapeutic purposes, the compounds of formula I may be employed in the form of their salts, it being understood that only those such salts should in practice be employed as contain anions or radicals that are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial physiological properties inherent in the parent compound are not vitiated by side-effects ascribable to those anions or radicals. Suitable acid addition salts include hydrohalides, for example, hydrochlorides, 8-chlorotheophyllinates, phosphates, nitrates, sulphates, maleates, fumarates, citrates, tartrates, methanesulphonates and ethanedisulphonates.

The following Examples illustrate the invention.

EXAMPLE I.

A mixture of 1-amino-2,2,6-6-tetramethylpiperidine (5.0 g.) and formaldehyde (3.0 ml. of 40% w/v solution) was shaken together for 10 minutes, the temperature rising spontaneously to 40° C. After cooling, the turbid solution was extracted with ether. The ethereal extract was dried and evaporated, and the residue was distilled *in vacuo*. 1-Methyleneamino - 2,2,6,6 - tetramethylpiperidine (3.6 g.) was obtained as a colourless liquid, b.p. 70° C./10 mm. Treatment of an ethereal solution of the base with alcoholic hydriodic acid gave the hydriodide salt as a cream microcrystalline solid, m.p. 154° C. (dec.).

EXAMPLE II.

To an ice cooled solution of 1-amino-2,2,6,6-tetramethylpiperidine (5.0 g.) in ether (10 ml.) was added acetaldehyde (1.41 g.), heat was evolved and water began to separate. Dried magnesium sulphate (2 g.) was added and the mixture was allowed to stand at room temperature for 18 hours. The mixture was filtered and the ethereal filtrate evaporated. The residue was distilled *in vacuo* to give 1-ethylideneamino - 2,2,6,6 - tetramethylpiperidine (5.3 g.) as a colourless liquid, b.p. 73—77° C./10 mm. The hydriodide salt, prepared as above, was a white crystalline solid, m.p. 204—208° C.

The present invention also provides as a still further feature pharmaceutical compositions comprising one or more of the compounds of formula I, or a salt thereof, and a significant amount of a pharmaceutical carrier which may be either a solid material or a liquid. The invention includes especially such compositions made up for oral or parenteral administration. In clinical practice the compounds of the present invention will normally be administered orally so that compositions suitable for oral administration are preferred.

Solid compositions for oral administration include compressed tablets, pills, dispersible powders or granules. In such solid compositions one or more of the active compounds of the invention is or are admixed with at least one inert diluent such as calcium carbonate, potato starch, alginic acid, or lactose. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents, such as magnesium stearate.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water and liquid paraffin. Besides inert diluents such compositions may also comprise adjuvants, such as wetting and suspending agents, and sweetening and flavouring agents.

The compositions according to the invention, for oral administration, also include capsules of absorbable material such as gelatin containing one or more of the active substances of the invention with or without the addition of diluents or excipients.

Preparations according to the invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. These compositions may also contain adjuvants such as wetting, emulsifying and dispersing agents. They may be sterilised by, for example, filtration through a bacteria-retaining filter, by incorporation in the compositions of sterilising agents, by irradiation, or by heating. They may also be manufactured in the form of sterile solid compositions, which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously several unit dosage forms may be administered at about the same time. In general, the preparations of the present invention should normally contain at least 0.025% by weight of active substance in the case of injectable solutions and at least 0.1% by weight of such substance in the case of oral preparations.

The following Examples will serve to illustrate pharmaceutical compositions according to the invention.

EXAMPLE III.

Tablets of the formula:

1-Methyleneamino-2,2,6,6-tetramethylpiperidine hydrogen tartrate	2.5 mg.
Lactose	87.3 mg.
Maize starch	5.0 mg.
Sodium carboxymethyl cellulose	0.2 mg.
Stearic acid	5.0 mg.

are prepared by dissolving 1-methyleneamino - 2,2,6,6 - tetramethylpiperidine hydrogen tartrate in water and dispersing the sodium carboxymethyl cellulose in the solution. The solution so obtained is then mixed with an intimate mixture of the lactose and starch and the resulting mass passed through a 12-mesh sieve. The resulting granules are dried overnight at 70° C. and then passed through a 16-mesh sieve. The stearic acid is added at this stage as a lubricant. These granules are then compressed into tablets.

EXAMPLE IV.

An injectable solution of the formula:

1-Methyleneamino-2,2,6,6-tetramethylpiperidine hydrochloride	0.25 g.
Distilled water	up to 100 ml.

is prepared by dissolving the 1-methyleneamino - 2,2,6,6 - tetramethylpiperidine hydrochloride in the distilled water. The solution is filtered and filled into ampoules which are sterilised in an autoclave.

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